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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,374	02/24/2004	Marshall L. Summar	1242/58	1629

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EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
09/27/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/785,374	SUMMAR ET AL.	
	Examiner	Art Unit	
	DIANA JOHANNSEN	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *43-54* is/are pending in the application.

5a) Of the above claim(s) *50-54* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *43-49* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0810;0311;0611*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 17, 2011 has been entered. All claims previously pending and under consideration have been canceled, and claims 43-54 are newly added. Claims 50-54 have been withdrawn (see paragraphs 2-3, below) and claims 43-49 are under consideration herein. It is noted that all prior rejections are moot in view of the cancellation of all claims previously under consideration. Applicant's remarks of February 28, 2011 have also been reviewed and considered, but are moot in view of the new grounds of rejection applied against the new claims.

Election/Restrictions

2. Claims 43-49 correspond to the species of the invention elected November 17, 2009 i.e., pulmonary hypertension) and are therefore under consideration herein. Although new claims 50-54 are considered as being directed to a species of the same invention as that of claims 43-49 (as indicated in the Restriction/Election of April 15, 2009 and reiterated in the prior Office action of March 2, 2010), because the species of claims 43-49 is not free of the prior art, a further search of the species of claims 50-54 has not been conducted.

3. Claims 50-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 17, 2009.

Information Disclosure Statement

4. The information disclosure statement filed March 17, 2011 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it provides incomplete citations (e.g., citations missing dates and other required identifying information) for several references. Accordingly, the following cite nos. were not marked as considered: 49-68 and 72. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

5. The information disclosure statement filed June 1, 2011 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Particularly, copies of the documents corresponding to cite nos. 19 and 82 were not provided, and therefore those documents have not been considered. It is also noted that the examiner has corrected the citation for document cite no. 17.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 43-44 and 47-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Kilbourn et al (US 5,334,380 [2 August 1994]; cited herein).

Kilbourn et al disclose the intravenous administration of citrulline to an animal subject, including a human patient (see entire reference, particularly col 5, line 34-col 6, line 33, as well as col 7, lines 1-8; col 8, lines 1-10; 31-38; claims 4-5, 11, 17). Regarding the claim limitation "subject in need thereof," it is noted that the specification does not define this terminology, and that any mammalian subject could reasonably be considered as "in need of" prevention of pulmonary hypertension in view of the health risks associated therewith; thus, the subjects of Kilbourn et al are sufficient to meet the requirements of the claims. Regarding the preamble limitation "of treating or preventing pulmonary hypertension," , MPEP 2111.02 states that:

> If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999).

Further, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where

the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In the instant case, the claims requires a single step of administering citrulline intravenously, and there is no manipulative difference between applicants' claimed method and that of Kilbourn et al.

Further, to the extent that intravenous administration of citrulline achieves the objective of "treating or preventing pulmonary hypertension," this is an inherent characteristic of the method, such that the method disclosed by Kilbourn et al meets the requirements of the claims. As discussed in MPEP 2112, the discovery of a new property or benefit of an old method does not render that method patentable (and further there "is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference" [MPEP 2112 II citing *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)]). In the instant case, it is particularly noted that Kilbourn et al disclose the use of citrulline at a concentration of "about 1 g/l to about 2 g/l" (see, e.g., col 5, lines 46-56; col 6, lines 23-26), meeting the requirements of dependent claims 47-48. Thus, Kilbourn et al disclose a method that inherently meetings the requirements of claims 43-44 and 47-48.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 43-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCaffrey et al (Biol Neonate 67:240-243 [1995]; cited in IDS) in view of Kaesemeyer (US Patent No. 5,767,160A [16 June 1998]; previously cited).

McCaffrey et al disclose treating infants with persistent pulmonary hypertension of the newborn (PPHN) via an intravenous infusion of 500 mg/kg L-arginine (see entire reference). Each infant so treated had been diagnosed with PPHN and thus constituted a subject "in need" of such treatment. McCaffrey et al teach all elements of claims 43-49 with the exception of the use of citrulline in place of arginine. Kaesemeyer teaches the use of arginine and its "biological equivalent" citrulline in the treatment of pulmonary

hypertension in any mammalian subject (see entire reference, particularly col 2, lines 20-23; col 3, lines 32-33; col 4 lines 36-60, col 5, line, 54-col 6, lines 45; claims 3, 10). Kaesemeyer disclose and exemplify the IV administration of arginine to subjects including dogs and humans (col 8, lines 14-64 and Examples).

In view of the teachings of Kaesemeyer, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted citrulline for arginine in the method of McCaffrey. As Kaesemeyer teaches that citrulline is the biological equivalent of arginine in methods including the treatment of pulmonary hypertension, an ordinary artisan would have recognized this modification as the simple substitution of one known therapy for another to achieve the predictable result of treating PPHN in an infant. With further regard to the dosages of claims 47-49, an ordinary artisan would have been further motivated to have employed the same dosage of citrulline as it taught by McCaffrey et al for arginine because Kaesemeyer teaches that citrulline is a biological equivalent that may be substituted in their methods for arginine. Thus, the dosage of 500 mg/kg (as taught by McCaffrey et al), which is embraced by claims 47-49, would have been obvious to one of ordinary skill in the art.

11. Claims 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaesemeyer (US Patent No. 5,767,160A [16 June 1998]; previously cited).

Kaesemeyer teaches the use of arginine and its "biological equivalent" citrulline in the treatment of pulmonary hypertension in any mammalian subject (see entire reference, particularly col 2, lines 20-23; col 3, lines 32-33; col 4 lines 36-60, col 5, line, 54-col 6, lines 45; claims 3, 10). Kaesemeyer disclose and exemplify the IV

administration of arginine to subjects including dogs and humans (col 8, lines 14-64 and Examples). It is noted that subjects being treated for pulmonary hypertension would be considered by one of ordinary skill in the art to constitute a group of subjects "in need" of therapy for pulmonary hypertension.

In view of Kaesemeyer's own teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted citrulline for arginine in the method of Kaesemeyer (and thereby to have performed a method meeting the requirements of the claims). As Kaesemeyer teaches that citrulline is the biological equivalent of arginine and teach substituting citrulline for arginine in methods including the treatment of pulmonary hypertension, an ordinary artisan would have recognized this modification as the simple substitution of one known therapy for another to achieve the predictable result of treating pulmonary hypertension in a subject (including a human subject).

12. Claims 45-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaesemeyer as applied to claims 43-44, above, and further in view of McCaffrey et al (Biol Neonate 67:240-243 [1995]; cited in IDS).

The teachings of Kaesemeyer are set forth in the preceding paragraph. Kaesemeyer do not teach the practice of their methods on an infant human (as required by claim 45), or on a subject with persistent pulmonary hypertension (as required by claim 46), and do not teach citrulline dosages meeting the requirements of claims 47-49.

McCaffrey et al disclose treating infants with persistent pulmonary hypertension of the newborn (PPHN) via an intravenous infusion of 500 mg/kg L-arginine (see entire reference). Each infant so treated had been diagnosed with PPHN and thus constituted a subject "in need" of such treatment.

In view of the teachings of Kaesemeyer and McCaffrey, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have treated infants with PPHN with 500 mg/kg of IV citrulline. Kaesemeyer teaches that arginine and citrulline are biological equivalents in the treatment of pulmonary hypertension. Thus, the teachings of Kaesemeyer are sufficient to suggest the use of either arginine or citrulline in the treatment of any known type of pulmonary hypertension, including PPHN in infants, as taught by McCaffrey et al. With regard to claims 57-59, McCaffrey et al teach that an appropriate dosage of IV arginine for use in infants is 500 mg/kg. As Kaesemeyer teaches the substitution of citrulline for the biologically equivalent arginine, absent a showing of unexpected results, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have employed the same type of dosage for citrulline as for arginine (i.e., 500 mg/kg, which is embraced by each of claims 47-49).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DIANA JOHANNSEN whose telephone number is (571)272-0744. The examiner can normally be reached on Monday-Friday, 8:30 am-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571/272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634